PATENT COOPERATION TREATY

PCT

INTERNATIONAL PRELIMINARY EXAMINATION REPORT

(PCT Article 36 and Rule 70)

Applicant's or agent's file reference 29140/BN/AT	**FOR FURTHER ACTION**	See Notification of Transmittal of International Preliminary Examination Report (Form PCT/IPEA/416)
International application No. PCT/SE97/01515	International filing date *(day/month/year)* 09.09.1997	Priority date *(day/month/year)* 11.09.1996
International Patent Classification (IPC) or national classification and IPC_6 C 07 K 14/085, A 61 K 39/125, G 01 N 33/569		
Applicant Niklasson, Bo		

1. This international preliminary examination report has been prepared by this International Preliminary Examining Authority and is transmitted to the applicant according to Article 36.

2. This REPORT consists of a total of 6 sheets, including this cover sheet.

   ☒ This report is also accompanied by ANNEXES, i.e., sheets of the description, claims and/or drawings which have been amended and are the basis for this report and/or sheets containing rectifications made before this Authority (see Rule 70.16 and Section 607 of the Administrative Instructions under the PCT).

   These annexes consist of a total of 4 sheets.

3. This report contains indications relating to the following items:

   - I ☒ Basis of the report
   - II ☐ Priority
   - III ☒ Non-establishment of opinion with regard to novelty, inventive step and industrial applicability
   - IV ☐ Lack of unity of invention
   - V ☒ Reasoned statement under Article 35(2) with regard to novelty, inventive step or industrial applicability; citations and explanations supporting such statement
   - VI ☐ Certain documents cited
   - VII ☐ Certain defects in the international application
   - VIII ☒ Certain observations on the international application

Date of submission of the demand	Date of completion of this report
06.04.1998	12.16.1998
Name and mailing address of the IPEA/SE Patent- och registreringsverket Box 5055 S-102 42 STOCKHOLM Telex 17978 PATOREG-S Facsimile No. 08-667 72 88	Authorized officer Carl-Olof Gustafsson Telephone No. 08-782 25 00

Form PCT/IPEA/409 (cover sheet) (January 1994)

INTERNATIONAL PRELIMINARY EXAMINATION REPORT

International application No.
PCT/SE97/01515

I. Basis of the report

1. This report has been drawn on the basis of *(Replacement sheets which have been furnished to the receiving Office in response to an invitation under Article 14 are referred to in this report as "originally filed" and are not annexed to the report since they do not contain amendments.)*:

☐ the international application as originally filed.

☒ the description, pages 1-27, as originally filed,
pages _____, filed with the demand,
pages _____, filed with the letter of _____.
pages _____, filed with the letter of _____.

☒ the claims, Nos. _____, as originally filed,
Nos. _____, as amended under Article 19,
Nos. _____, filed with the demand,
Nos. 1-14, filed with the letter of 22.10.1998,
Nos. _____, filed with the letter of _____.

☐ the drawings, ~~sheets~~/fig _____, as originally filed,
~~sheets~~/fig _____, filed with the demand
~~sheets~~/fig _____, filed with the letter of _____,
~~sheets~~/fig _____, filed with the letter of _____.

2. The amendments have resulted in the cancellation of:

☐ the description, pages _____
☐ the claims, Nos. _____
☐ the drawings, ~~sheets~~/fig _____

3. ☐ This report has been established as if (some of) the amendments had not been made, since they have been considered to go beyond the disclosure as filed, as indicated in the supplemental Box (Rule 70.2(c)).

4. Additional observations, if necessary:

INTERNATIONAL PRELIMINARY EXAMINATION REPORT

International application No.
PCT/SE97/01515

III. Non-establishment of opinion with regard to novelty, inventive step and industrial applicability

The questions whether the claimed invention appears to be novel, to involve an inventive step (to be non obvious), or to be industrially applicable have not been examined in respect of:

☐ the entire international application,

☒ claims Nos. 13 and 14

because:

☒ the said international application, or the said claims Nos. 13 and 14 relate to the following subject matter which does not require an international preliminary examination *(specify)*:

See PCT Rule 67.1(iv): Methods for treatment of the human or animal body by surgery or therapy, as well as diagnostic methods.

☐ the description, claims or drawings *(indicate particular elements below)* or said claims Nos. _____ are so unclear that no meaningful opinion could be formed *(specify)*:

☐ the claims, or said claims Nos. _____ are so inadequately supported by the description that no meaningful opinion could be formed.

☐ no international search report has been estabilised for said claims Nos. _____.

INTERNATIONAL PRELIMINARY EXAMINATION REPORT

International application No.
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V. Resoned statement under Article 35(2) with regard to novelty, inventive step or industrial applicability; citations and explanations supporting such statement

1. Statement

Novelty (N)	Claims	1-4,7-12	YES
	Claims	5,6	NO
Inventive step (IS)	Claims	1-4,7-12	YES
	Claims	5,6	NO
Industrial applicability (IA)	Claims	1-12	YES
	Claims		NO

2. Citations and explanations

The application pertains to "Ljungan picornavirus", vaccines and assays, the virus comprising a noncoding region in its viral genome, the nucleotide sequence of which corresponds to SEQ ID No 1 or homologous sequences having at least 75 % homology, and further causing mammalian disease.

In many countries the expression "Ljungan picornavirus", which, according to the description, is a novel type of picornaviruses that can be reproducibly isolated from the environment, is considered to limit the claims to such viruses and variants or fragments thereof having essentially the same functional characteristics. The protective scope of the claims would thereby be defined.

In other countries, the ref. to "Ljungan picornavirus" would not limit the claims to the general features mentioned in the description. The protective scope of claim 1 may then include e.g. a hybrid virus construct comprising the noncoding sequence inserted in any known disease causing picornavirus to be used for vaccine production. Claims covering such viruses would lack an inventive step.

The International Search Report revealed a few documents of relevance. Thus Hyypiä T, Proc. Natl. Acad. Sci. vol 89, 1992, pp 8847-51 refer to echovirus 22 (parecho 1) with minor structural similarities to the Ljungan virus, yet having a local sequence homology of about 75% in the VP3 region (see fig 2, positions 1970-2060 and 2210-2300). At least this region is considered have the ability to produce crossreactive antibodies. These antibodies, covered by claims 5 and 6, would therefore lack novelty.

.../...

Supplemental Box
(To be used when the space in any of the preceding boxes is not sufficient)

Continuation of: V

Jun HS et al., J. Gen. Virol. vol. 76, 1995, pp 2557-66 and Dan K et al., Exp. Anim. vol 44, 1995, pp 211-18 refer to encephalomyocarditis viruses (EMCV) involved in diabetes. The refs. show that antibodies to structural proteins of the virus can be used for serological assays and that recombinant structural proteins can be used in immunisation in diabetes mellitus and myocarditis.

However, according to the applicant, a sequence comparison of the coding parts with EMC viruses shows that they lack any homology with the "Ljungan virus". Novelty is therefore considered to be present also for antibodies to the virus, provided that it can be shown that no crossreactivity of technical relevance exists to the related viruses (see Hyypiä T) Inventive Step and industrial applicability are acknowledged in view of the obvious diagnostic and immunological features of the novel viruses. Thus claims 1-4 and 7-12 are considered to fullfil the requirements of novelty, inventiv step and industrial applicability.

Patent claims taken singly as well as in totality, must be clear and concise (PCT Article 6) in order to enable potential users to ascertain, without undue burden, the scope of protection. Due to this definition of the virus in claim 1, it would involve an undue burden to the public to reveal the scope of protection.
Therefore, claims 1-3 and 5-12 do not fulfil the requirements of clarity and conciseness according to PCT Rule 6.1(a).

VIII. Certain observations on the international application

The following observations on the clarity of the claims, description, and drawings or on the question whether the claims are fully supported by the description, are made:

In many countries a complex definition of a subject in the description can be implicitly referred to in the claims by a simple reference to that subject in the claims. In other countries this is not accepted and the definition must be included in the claims even if it is quite laborious. The following remarks therefore applies only in countries which would not accept such a reference in a claim.

The general approach of claim 1 is to describe a virus by only a fragment of its genome or a fragment of its structural proteins, and broadening this definition by stating that it may also include a virus with 75% homology, without linking this definition to any distinguishing features of the original virus, is not considered to provide a clear and concise definition.
The absence of explicit restrictions limiting claims to a virus, that has the relevant attributes referred to in the description, and the absence of an indication that the noncoding sequence provides an unexpected valuable feature to the virus makes the scope of protection uncertain. The level of homology referred to in claims 1 and 2 seems to be of less importance as it refers to a noncoding region and has not been shown to be related to any immunological, biochemical or biological features of relevance to the virus.

L (MED94)
UI - 96357444
AU - Hirasawa K
AU - Ogiso Y
AU - Takeda M
AU - Lee MJ
AU - Itagaki S
AU - Doi K
TI - Protective effects of macrophage-derived interferon against encephalomyocarditis virus-induced diabetes mellitus in mice.
LA - Eng
MH - Animal
MH - Cardiovirus Infections/*PREVENTION & CONTROL/PHYSIOPATHOLOGY
MH - Carrageenan/PHARMACOLOGY
MH - Cells, Cultured
MH - Diabetes Mellitus, Experimental/*PREVENTION & CONTROL/PHYSIOPATHOLOGY
MH - Disease Models, Animal
MH - Dose-Response Relationship, Drug
MH - *Encephalomyocarditis Virus
MH - Gram-Positive Bacterial Infections
MH - In Vitro
MH - Interferons/ANTAGONISTS & INHIB/*PHYSIOLOGY
MH - Islets of Langerhans/DRUG EFFECTS
MH - Macrophages, Peritoneal/DRUG EFFECTS/*METABOLISM
MH - Male
MH - Mice
MH - Mice, Inbred BALB C
MH - Mice, Inbred C57BL
MH - Propionibacterium acnes/PHYSIOLOGY
RN - 9000-07-1 (Carrageenan)
RN - 9008-11-1 (Interferons)
AD - Department of Biomedical Science, Faculty of Agriculture, University of Tokyo, Japan.
AB - The involvement of macrophages in protection against diabetes mellitus in mice of BALB/c (susceptible) and C57BL (resistant) strains infected with the B (non-diabetogenic) or D (highly diabetogenic) variant of encephalomyocarditis (EMC) virus was examined. Pretreatment with the B variant of EMC virus (EMC-B), avirulent interferon (IFN) inducer, or Corynebacterium parvum inhibited diabetes in BALB/c mice infected with the D variant of EMC virus (EMC-D). Treatment of C57BL mice with carrageenan to compromise macrophage function rendered C57BL mice susceptible to EMC-D-induced diabetes. In macrophage culture for BALB/c mice, EMC-B induced IFN at an earlier stage than did EMC-D. The C57BL mouse-derived macrophages produced more IFN than did BALB/c mouse-derived macrophages after stimulation with EMC-D. Moreover, C. parvum increased IFN production in macrophage cultures from BALB/c mice, whereas carrageenan inhibited that in macrophage cultures from C57BL mice. These results suggest that IFN derived from macrophages may have an important role in protecting mice against EMC virus infection.
SO - Lab Anim Sci 1995 Dec;45(6):652-6

y

6 (MED94)
UI - 96035445
AU - Dan K
AU - Seto Y
AU - Fujita T
AU - Asaba Y
AU - Takei I
AU - Fujita H
AU - Kato R
TI - Characterization of insulin-dependent diabetes mellitus induced by a new variant (DK-27) of encephalomyocarditis virus in DBA/2 mice.
LA - Eng
MH - Animal
MH - Blood Glucose/ANALYSIS
MH - Cardiovirus Infections/*COMPLICATIONS/METABOLISM/PATHOLOGY
MH - *Diabetes Mellitus, Insulin-Dependent/ETIOLOGY/METABOLISM/PATHOLOGY/VIROLOGY
MH - Disease Models, Animal
MH - *Encephalomyocarditis Virus/PHYSIOLOGY
MH - Glucagon/ANALYSIS
MH - Hemoglobin A, Glycosylated/ANALYSIS
MH - Hyperglycemia/ETIOLOGY
MH - Insulin/BLOOD
MH - Male
MH - Mice

MH - Mice, Inbred DBA
MH - Pancreas/CHEMISTRY/PATHOLOGY/VIROLOGY
MH - Virus Replication
RN - 0 (Blood Glucose)
RN - 0 (Hemoglobin A, Glycosylated)
RN - 11061-68-0 (Insulin)
RN - 9007-92-5 (Glucagon)
AD - Division of Chemotherapy, School of Medicine, Keio University, Tokyo, Japan.
AB - A murine diabetes mellitus induced with a new diabetogenic variant (DK-27) which we isolated from the M variant of the encephalomyocarditis (EMC) virus was characterized. Male DBA/2 mice (9.5 weeks old) were infected with various infectious doses of DK-27 intraperitoneally. Blood glucose and insulin levels were examined in association with the viral replication. Pancreatic pathology and hormone contents and stable hemoglobin A1c (St-A1c) levels were also examined on the final day of observation (35 days of post-infection). In infected mice, blood glucose levels rapidly elevated at 72 hr, slightly decreased between 7 and 10 days and finally became sustained hyperglycemia. On the other hand, blood insulin levels elevated at 48 hr, promptly decreased, and subsequently became sustained hypoinsulinemia. Viral replication in pancreases reached the highest titers at 48 hr and rapidly disappeared with all infectious doses used. Pancreatic insulin contents in infected mice were not detectable, and glucagon contents were not affected. In pathological examination, atrophy of islets and marked diminution of B-cells were observed, and A-cells occupied the major part of an infected islet. St-A1c levels reflected lasting hyperglycemia. These findings show that DK-27 causes insulin-dependent diabetes mellitus by the specific and direct destruction of pancreatic B-cells in susceptible mice. Such a diabetic model mouse will be useful for therapeutic studies.
SO - Exp Anim 1995 Jul;44(3):211-8

AU - Yoon SW
AU - Kang Y
AU - Pak CY
AU - Lee MC
AU - Yoon JW
TI - Cloning and expression of the VP1 major capsid protein of diabetogenic encephalomyocarditis (EMC) virus and prevention of EMC virus-induced diabetes by immunization with the recombinant VP1 protein.
LA - Eng
MH - Amino Acid Sequence
MH - Animal
MH - Base Sequence
MH - Capsid/CHEMISTRY/*GENETICS/*IMMUNOLOGY
MH - Cardiovirus Infections/*COMPLICATIONS/VIROLOGY
MH - Diabetes Mellitus, Experimental/*PREVENTION & CONTROL/VIROLOGY
MH - Diabetes Mellitus, Insulin-Dependent/PREVENTION & CONTROL/VIROLOGY
MH - Encephalomyocarditis Virus/GENETICS/*IMMUNOLOGY
MH - Genes, Structural, Viral/*GENETICS
MH - Insulin/ANALYSIS
MH - Islets of Langerhans/PATHOLOGY
MH - Male
MH - Mice
MH - Molecular Sequence Data
MH - Recombinant Fusion Proteins/BIOSYNTHESIS/IMMUNOLOGY
MH - Sequence Analysis, DNA
MH - Support, Non-U.S. Gov't
MH - Vaccination
MH - Viral Vaccines/IMMUNOLOGY
RN - 0 (Capsid)

RN - 0 (Recombinant Fusion Proteins)
RN - 0 (Viral Vaccines)
RN - 0 (VP1 protein, encephalomyocarditis virus)
RN - 11061-68-0 (Insulin)
AD - Department of Microbiology and Infectious Diseases, Faculty of Medicine, University of Calgary, Alberta, Canada.
AB - The development of diabetes in mice induced by encephalomyocarditis (EMC) virus provides the best experimental evidence that viruses have an aetiological role in the pathogenesis of this disease. The major capsid protein (VP1) of EMC virus is important for both the attachment of the virus to pancreatic beta cells and for the determination of antigenicity. This experiment was initiated to clone the gene for the major capsid protein, VP1, of the diabetogenic EMC (EMC-D) virus, express the VP1 protein, and test whether the recombinant VP1 protein can prevent development of EMC-D virus-induced diabetes in mice. We successfully cloned the VP1 gene of the EMC-D virus in the expression vector pRSET and subsequently expressed the protein in Escherichia coli. The recombinant VP1 protein was then purified by affinity chromatography. Five- to six-week-old male SJL/J mice were immunized intraperitoneally with purified VP1 protein and then challenged after various intervals with highly diabetogenic EMC-D virus. None of the VP1-immunized mice developed diabetes, irrespective of the interval between immunization and virus challenge, whereas 80 to 95% of the EMC-D virus-infected control mice did develop diabetes. All of the VP1-immunized mice showed intact pancreatic islet architecture, whereas most of the infected control mice showed severe beta cell necrosis and lymphocytic infiltration of their pancreatic islets. On the basis of these observations, we conclude that the recombinant VP1 protein of EMC-D virus can completely prevent the development of EMC-D virus-induced diabetes in mice.
SO - J Gen Virol 1995 Oct;76 (Pt 10):2557-66
.. continue printing? (Y/N)

Copy for the Elected Office (EO/US) PCT/SE97/01515

PATENT COOPERATION TREATY

From the INTERNATIONAL BUREAU

PCT

NOTIFICATION OF THE RECORDING OF A CHANGE

(PCT Rule 92bis.1 and Administrative Instructions, Section 422)

To:

NILSSON, Brita
AB Stockholms Patentbyrå Zacco & Bruhn
P.O. Box 23101
S-104 35 Stockholm
SUÈDE

Date of mailing (day/month/year)
22 February 1999 (22.02.99)

Applicant's or agent's file reference
29140/BN/AT

IMPORTANT NOTIFICATION

International application No.
PCT/SE97/01515

International filing date (day/month/year)
09 September 1997 (09.09.97)

1. The following indications appeared on record concerning:

[X] the applicant [X] the inventor [ ] the agent [ ] the common representative

Name and Address
NIKLASSON, Bo
Sibyllegatan 15
S-114 42 Stockholm
Sweden

State of Nationality: SE
State of Residence: SE
Telephone No.:
Facsimile No.:
Teleprinter No.:

2. The International Bureau hereby notifies the applicant that the following change has been recorded concerning:

[X] the person [X] the name [X] the address [ ] the nationality [ ] the residence

Name and Address
APODEMUS AB
Sibyllegatan 15
S-11442 -Stockholm
Sweden

State of Nationality: SE
State of Residence: SE
Telephone No.:
Facsimile No.:
Teleprinter No.:

3. Further observations, if necessary:

4. A copy of this notification has been sent to:

[X] the receiving Office
[ ] the International Searching Authority
[X] the International Preliminary Examining Authority
[ ] the designated Offices concerned
[X] the elected Offices concerned
[ ] other:

The International Bureau of WIPO
34, chemin des Colombettes
1211 Geneva 20, Switzerland
Facsimile No.: (41-22) 740.14.35

Authorized officer
Athina Nickitas-Etienne
Telephone No.: (41-22) 338.83.38

PATENT COOPERATION TREATY

From the INTERNATIONAL BUREAU

PCT

NOTIFICATION OF ELECTION

(PCT Rule 61.2)

To:

United States Patent and Trademark Office
(Box PCT)
Crystal Plaza 2
Washington, DC 20231
ETATS-UNIS D'AMERIQUE

in its capacity as elected Office

Date of mailing (day/month/year) 06 May 1998 (06.05.98)	
International application No. PCT/SE97/01515	**Applicant's or agent's file reference** 29140/BN/AT
International filing date (day/month/year) 09 September 1997 (09.09.97)	**Priority date** (day/month/year) 11 September 1996 (11.09.96)
Applicant NIKLASSON, Bo	

1. The designated Office is hereby notified of its election made:

   [X] in the demand filed with the International Preliminary Examining Authority on:

   06 April 1998 (06.04.98)

   [ ] in a notice effecting later election filed with the International Bureau on:

2. The election [X] was

   [ ] was not

   made before the expiration of 19 months from the priority date or, where Rule 32 applies, within the time limit under Rule 32.2(b).

The International Bureau of WIPO **34, chemin des Colombettes** **1211 Geneva 20, Switzerland**	Authorized officer Athina Nickitas-Etienne
Facsimile No.: (41-22) 740.14.35	Telephone No.: (41-22) 338.83.38

PATENT COOPERATION TREATY

From the INTERNATIONAL BUREAU

PCT

NOTIFICATION OF THE RECORDING OF A CHANGE

(PCT Rule 92bis.1 and Administrative Instructions, Section 422)

To:

NILSSON, Brita
AB Stockholms Patentbyrå Zacco & Bruhn
P.O. Box 23101
S-104 35 Stockholm
SUEDE

Date of mailing (day/month/year)
03 August 1998 (03.08.98)

Applicant's or agent's file reference
29140/BN/AT

IMPORTANT NOTIFICATION

International application No.
PCT/SE97/01515

International filing date (day/month/year)
09 September 1997 (09.09.97)

1. The following indications appeared on record concerning:

[ ] the applicant [ ] the inventor [X] the agent [ ] the common representative

Name and Address
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2. The International Bureau hereby notifies the applicant that the following change has been recorded concerning:

[ ] the person [ ] the name [X] the address [ ] the nationality [ ] the residence

Name and Address
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S-104 35 Stockholm
Sweden

State of Nationality:
State of Residence:
Telephone No.: +46 8 729 95 00
Facsimile No.: +46 8 31 83 15
Teleprinter No.:

3. Further observations, if necessary:

4. A copy of this notification has been sent to:

[X] the receiving Office
[ ] the International Searching Authority
[X] the International Preliminary Examining Authority
[ ] the designated Offices concerned
[X] the elected Offices concerned
[ ] other:

The International Bureau of WIPO
34, chemin des Colombettes
1211 Geneva 20, Switzerland

Facsimile No.: (41-22) 740.14.35

Authorized officer
Catherine Massetti

Telephone No.: (41-22) 338.83.38